AN ASYMMETRIC SYNTHESIS OF THE ANT VENOM ALKALOID (3*S*,5*S*,8a*R*)-3-BUTYL-5-(4-PENTENYL)INDOLIZIDINE *VIA* THE SHARPLESS ASYMMETRIC DIHYDROXYLATION#

Hiroki Takahata,* Hiroshi Bandoh, and Takefumi Momose*

Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

Abstract- The first asymmetric synthesis of the ant venom alkaloid (3*S*,5*S*,8a*R*)-3-butyl-5-(4-pentenyl)indolizidine (**1**) has been performed by starting with the Sharpless asymmetric dihydroxylation of *N*-alkenylcarbamate (**3**) followed by reductive annulation (5-exo-tetrahedral).

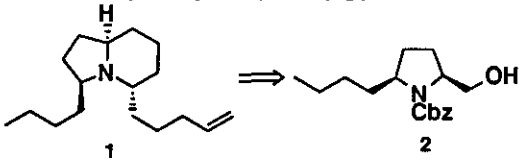
Indolizidine alkaloids offer attractive targets for synthesis because of their unique structures and intriguing biological activities.[1] Recently, a novel 3,5-dialkylated indolizidine (**1**) was isolated from the ant venom of *Monomorium smithii*.[2] Its absolute configuration and potential biological activities, however, remain unknown owing to its short supply from natural sources. So far, the synthesis of **1** has been reported only once in its racemic form,[2] and its chiral synthesis has never been performed. Our interest in this field is directed towards the synthetic utilization of the Sharpless asymmetric dihydroxylation (AD) reaction,[3] as employed for the enantioselective construction of oxygen[4] and nitrogen[5] heterocycles leading to natural products. In this communication, we impart the first asymmetric synthesis of **1** *via* construction of *cis*-2,5-disubstituted pyrrolidine by capitalizing on AD reaction as a crucial step of a homochiral 4-pentenylcarbamate available from L-norleucine.

Recent investigations in this laboratory have disclosed that the kinetically controlled amidomercuration of α-

---

This paper is dedicated to the memory of the late Professor Yoshio Ban.

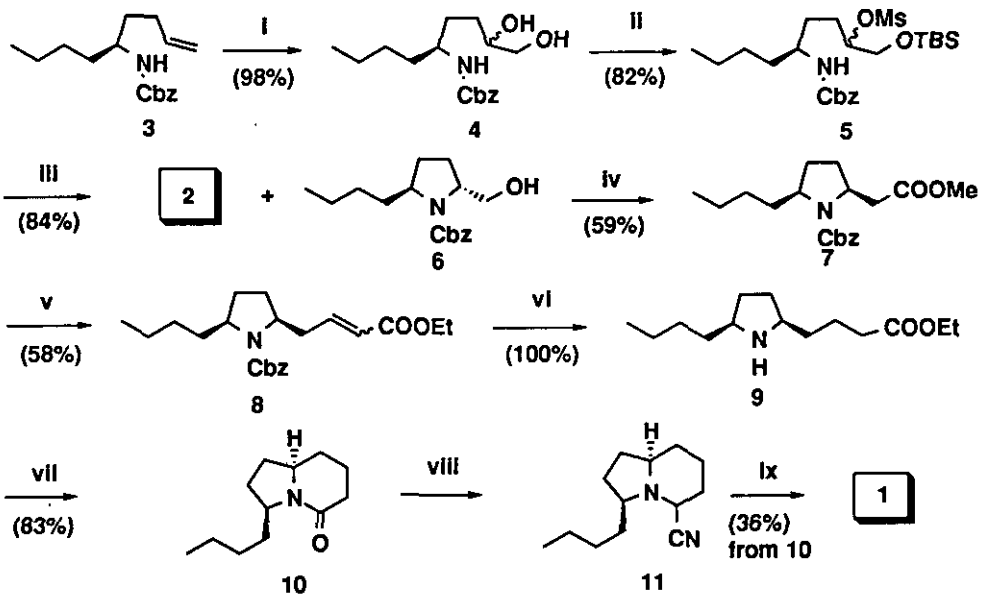
amino acids-derived α-alkylated 4-pentenylcarbamates resulted in stereoselective cyclization (5-*exo-trig*) and provided the *trans*-2-alkyl-5-(hydroxymethyl)pyrrolidine. The latter has been converted to several biologically active nitrogen-containing compounds such as (+)-pyrrolidine 197B,[6a] (+)-xenovenine,[6b] and (+)-indolizidine 195B.[6c] This time we needed the *cis*-2-butyl-5-hydroxymethylpyrrolidine (**2**) for the preparation of **1**.



1 **2**

Unfortunately, examination of the various amidomercuration under thermodynamically controlled conditions resulted in *trans*-selectivity preferentially. Accordingly, our regard was focused on the Sharpless AD reaction as a step enforcing the introduction of a stereogenic center and subsequent stereoselective construction of the *cis*-pyrrolidine (**2**) by 5-*exo-tet* cyclization. Our synthesis of **1** began with the Sharpless AD reaction of (*S*)-*N*-benzyloxycarbonyl-1-butyl-4-pentenylamine (**3**), readily accessible from L-norleucine.[6a] Treatment of **3** with AD-mix-β (Aldrich No. 39,276-6) at 0 °C in *tert*-butyl alcohol/water (1:1) for 24 h afforded a diastereomeric mixture of the diols (**4**). Selective protection of the primary hydroxyl in **4** with *tert*-butyldimethylsilyl followed by mesylation of the secondary hydroxyl provided the mesylate (**5**). Exposure of **5** to an atmosphere of hydrogen in the presence of $Pd(OH)_2$ as a catalyst in methanol caused concurrent debenzyloxycarbonylation and annulation (5-*exo-tet*) to give the pyrrolidine salt, which was converted by a two-step sequence (i, de-*tert*-butyldimethylsilylation; ii, *N*-bezyloxycarbonylation) to a separable 4:1 mixture of the 2,5-*cis*-disubstituted pyrrolidine (**2**) and its *trans* isomer (**6**).

With the requisite **2** in hand, the elongation of its appendage was initiated. The Jones oxidation of **2** gave the acid, which on the subsequent Arndt-Eistert homologation provided the ester (**7**). Next, application of a three-step sequence (i, reduction; ii, the Swern oxidation; iii, the Horner-Emmons reaction) to **7** gave the α,β-unsaturated ester(**8**). Both debenzyloxycarbonylation and olefin reduction were effected by catalytic hydrogenation over $Pd(OH)_2$ of **8** to give **9**, but failed in further annulation into indolizidinone. The intramolecular lactamization of **9** was performed by the Weinreb's procedure[7] utilizing trimethylaluminum to give the synthetic intermediate (**10**). The spectral data for **10** were completely identical with those reported.[2] According to the Jones's method[2] described for the synthesis of (±)-**1** from (±)-**10**, **10** was converted *via* the amino nitrile to the desired (+)-(3*S*,5*S*,8a*R*)-3-butyl-5-(4-pentenyl)indolizidine (**1**)[8] (bp 65-70 °C/1 mmHg) $[\alpha]^{26}_D$ +71.4° (c 0.645, $CHCl_3$), whose spectral data were in accordance with those reported.[2,9]



i, AD-mix-β; ii, 1) TBSCl/imidazole/DMF; 2) MsCl/Et_3N; iii, 1) H_2/$Pd(OH)_2$; 2) 1% HCl;3) CbzCl/NaOH; iv, 1) CrO_3/H^+/acetone; 2) CH_2N_2; 3) AgCOOPh/MeOH; v, 1) $LiBH(Et)_3$; 2) $(COCl)_2$/DMSO/Et_3N; 3) $(EtO)_2P(O)CH_2COOEt$/NaH; vi, H_2/$Pd(OH)_2$; vii, Me_3Al; viii, 1) DIBALH; 2) 60% $HClO_4$; 3) KCN; ix; 1-pentenylmagnesium bromide

In conclusion, we have demonstrated the new construction of 2,5-*cis*-disubstituted pyrrolidine ring using the Sharpless asymmetric dihydroxylation as a key reaction and the first asymmetric synthesis of the ant venom alkaloid (**1**). Accordingly, this method provides a promising avenue to the voluntarily stereoselective synthesis of homochiral α,α'-disubstituted pyrrolidine and piperidine rings, which could be led the related biologically active compounds.

ACKNOWLEDGMENT

We are grateful to Professor K. B. Sharpless, The Scripps Research Institute, for providing us a manuscript copy of ref. 3a before its publication.

REFERENCES AND NOTES

1 H. Takahata and T. Momose, In *The Alkaloids*; G. A. Cordell, Ed., Academic Press: San Diego, 1993; Vol 44, pp. 189-256.

2 T. H. Jones, A. Laddago, A. W. Don, and M. S. Blum, *J. Nat. Prod.*, 1990, **53**, 375.

3 a) H. C. Kolb, M. S. VanNieuwehze, and K. B. Sharpless, *Chemical Reviews*, **1994**, 94, 2483; b) R. A. Johnson, and K. B. Sharpless, In *Catalytic Asymmetric Synhess*; I. Ojima, Ed., VCH Publishers Inc.: New York, 1993; pp. 227-272.

4 S. C. Sinha and E. Keinan, *J. Am. Chem. Soc.*, 1993, **115**, 4891; b) Idem, *J. Org. Chem.*, 1994, **59**, 949.

5 a) H. Takahata, K. Inose, and T. Momose, *Heterocycles*, 1994, **38**, 269; b) H. Takahata, K. Inose, N. Araya, and T. Momose, *Heterocycles*, 1994, **38**, 1961.

6 a) H. Takahata, H. Takehara, N. Ohkubo, and T. Momose, *Tetrahedron:Asymmetry*, 1990, **1**, 561; b) H. Takahata, H. Bandoh, and T. Momose, *J. Org. Chem.*, 1992, **57**, 4401; c) Idem, *Heterocycles*, 1993, **36**, 2777.

7 A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, 1977, 4171.

8 ^{1}H Nmr ($CDCl_3$) δ 0.91 (3 H, t, *J*= 7 Hz), 0.96-2.2 (12 H, m), 2.4-2.7 (2 H, br d), 3.0-3.2 (1H, m), 4.98(1H, br d, *J*= 10 Hz), 5.03 (1H, br d, *J*= 17 Hz), 5.7-5.9 (1 H, m); ^{13}C nmr ($CDCl_3$) δ 14.11, 19.32, 20.04, 23.10, 26.93, 27.73, 28.31, 28.77, 29.46, 32.43, 32.54, 34.07, 52.64, 56.27, 58.54, 114.44, 138.92.

9 The optical rotation of natural product (**1**) is not reported in ref.2.

Received, 6th January, 1995